Electrophysical agents (FS-08)

Jan Bjordal (Norway)
David Baxter (New Zealand)
Ernesto Leal Junior (Brazil)
Gladys Cheing (China)
Liisa Laakso (Australia)

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Why electrophysical agents (EPA) should substitute for simple analgesia in selected clinical applications

Jan M. Bjordal
Professor
University of Bergen & Bergen University College, Norway

President, International Society for ElectroPhysical Agents in Physiotherapy (ISEAPT)
THE SCOPE OF THE PROFESSION

Physiotherapy is defined by the Royal Charter as the four pillars of practice of:

- massage
- exercise and movement
- electrotherapy

The Royal Charter clearly identifies that the role of the CSP is to ‘foster and develop’ the use of these four pillars of practice.

Physical therapists must take responsibility to meet health service needs

- Many patients want non-drug alternatives for pain relief
- Polyparmacy is an increasing health problem
Why do we need electrophysical agents?
More rapid time/effect profiles in knee osteoarthritis
Inflammation is a major contributor to pain in OA

Inflammation with neutrophil cell migration

Inflammation in synovia

COX expression in all layers of cartilage

Terslev et al.  Ann Rheum Dis 2005

Brochhausen et al.  Arthr Ther Res 2006
Pain medication is widely used

The use of medication and nutritional supplements during FIFA World Cups 2002 and 2006

P Tscholl, A Junge and J Dvorak

Br. J. Sports Med. 2008;42;725-730; originally published online 28 Feb 2008;

Table 1  Number of players with reported medication and use of nutritional supplements

<table>
<thead>
<tr>
<th></th>
<th>WC 2002</th>
<th></th>
<th>WC 2006</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of players</td>
<td></td>
<td>No. of players</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Per match (n = 2944) (%)</td>
<td>During tournament (n = 736) (%)</td>
<td>Per match (n = 2944) (%)</td>
<td>During tournament (n = 736) (%)</td>
</tr>
<tr>
<td>Any medication</td>
<td>1335 (45.3)</td>
<td>500 (67.9)</td>
<td>1257 (42.7)</td>
<td>508 (68.0)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>950 (32.6)</td>
<td>403 (54.8)</td>
<td>855 (29.0)</td>
<td>399 (54.2)</td>
</tr>
<tr>
<td>Injections*</td>
<td>120 (4.1)</td>
<td>77 (10.5)</td>
<td>103 (3.5)</td>
<td>58 (7.9)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>131 (4.4)</td>
<td>91 (12.4)</td>
<td>108 (3.7)</td>
<td>83 (11.3)</td>
</tr>
<tr>
<td>β-2-Agonists</td>
<td>34 (1.2)</td>
<td>8 (1.1)</td>
<td>31 (1.1)</td>
<td>12 (1.6)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>60 (2.0)</td>
<td>43 (5.8)</td>
<td>105 (3.6)</td>
<td>55 (7.5)</td>
</tr>
<tr>
<td>Any supplement</td>
<td>925 (31.4)</td>
<td>314 (42.7)</td>
<td>1041 (35.4)</td>
<td>317 (43.1)</td>
</tr>
<tr>
<td>Any substance</td>
<td>1809 (61.4)</td>
<td>582 (79.1)</td>
<td>1868 (63.5)</td>
<td>600 (81.5)</td>
</tr>
</tbody>
</table>

*Corticosteroid and local anaesthetic injections only.
Pharmacological treatment of chronic pain

Breivik et al. 2005, Eur J Pain
Medication used in osteoarthritis

Medication for OA is usually NSAIDs, Cox-2s, painkillers or combinations thereof

Currently taking medicine as prescribed or recommended by doctor?

- Yes 71%
- No 29%

Number of prescribed/GP recommended medicines taken?

- 2+ medicines 43%
- 1 only 57%

Is this the only type of medicine taken?

- Yes, do not self-medicate 78%
- No, self-medicate as well 24%

Drug types used:
- NSAIDs (non-steroidal anti-inflammatories) (32%)
- Selective Cox-2 inhibitors (18%)
- Paracetamol (15%)

Percentage respondents

Base: All currently visiting their doctor about arthritis (1,149)

percentage respondents

Base: All receiving a prescription or doctor recommended medicine (812)

OA Nation survey UK 2003

JM Bjordal 2009
Oral NSAIDs in knee OA

Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials

Jan Magnus Bjordal, Anne Elisabeth Ljunggren, Atle Klovning, Lars Storløkken

BMJ 2004;329:1317-23; originally published online 23 Nov 2004; doi:10.1136/bmj.38273.628655.63

Table 2
Characteristics of trials of oral NSAIDs for pain relief in patients with knee osteoarthritis

<table>
<thead>
<tr>
<th>First author</th>
<th>Drug</th>
<th>No of patients on active drug</th>
<th>Method quality</th>
<th>Mean baseline pain (mm VAS)</th>
<th>Best mean difference (95% CI) of change over placebo (mm VAS)</th>
<th>Outcome time-points (in weeks, max. effect in bold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensen -99</td>
<td>Celecoxib-naproxen</td>
<td>597</td>
<td>5</td>
<td>54.1</td>
<td>8.0 (2.3 to 13.7)</td>
<td>2, 6, 12</td>
</tr>
<tr>
<td>Case -03</td>
<td>Diclofenac</td>
<td>25</td>
<td>4</td>
<td>39.6</td>
<td>11.7 (6.2 to 17.2)</td>
<td>2, 12</td>
</tr>
<tr>
<td>Detrembleur -05</td>
<td>Celecoxib</td>
<td>8</td>
<td>3</td>
<td>NA</td>
<td>11.5 (−12.7 to 35.7)</td>
<td>2</td>
</tr>
<tr>
<td>Dore -95</td>
<td>Naproxen-etoaca</td>
<td>168</td>
<td>3</td>
<td>NA</td>
<td>16.3 (4.8 to 27.7)</td>
<td>2, 4</td>
</tr>
<tr>
<td>Ehrlich -01</td>
<td>Rofecoxib</td>
<td>147</td>
<td>5</td>
<td>61.9</td>
<td>21.9 (15 to 28.7)</td>
<td>1, 2, 4, 6</td>
</tr>
<tr>
<td>Fleischmann -97</td>
<td>Nabumetone-naproxen</td>
<td>185</td>
<td>3</td>
<td>59.9</td>
<td>9.3 (0.7 to 17.6)</td>
<td>2, 4</td>
</tr>
<tr>
<td>Gibofsky -03</td>
<td>Celecoxib-etoaca</td>
<td>379</td>
<td>5</td>
<td>67.7</td>
<td>11.6 (3.4 to 19.8)</td>
<td>3, 6</td>
</tr>
<tr>
<td>Gottesdiener -02</td>
<td>Etoricoxib-diclofenac</td>
<td>226</td>
<td>5</td>
<td>68.4</td>
<td>18.4 (16.6 to 20.2)</td>
<td>1, 2, 4, 6</td>
</tr>
<tr>
<td>Kivitz -02</td>
<td>Valdecoxib-naproxen</td>
<td>408</td>
<td>5</td>
<td>71.9</td>
<td>5.5 (2.3 to 8.8)</td>
<td>2, 6, 12</td>
</tr>
<tr>
<td>Kivitz -04</td>
<td>Naproxen-nabumetone</td>
<td>824</td>
<td>5</td>
<td>74.5</td>
<td>15.1 (4.9 to 25.3)</td>
<td>1, 6</td>
</tr>
<tr>
<td>Lee -85</td>
<td>Diflunisal</td>
<td>279</td>
<td>3</td>
<td>57</td>
<td>8.5 (−2.9 to 19.5)</td>
<td>3, 6</td>
</tr>
<tr>
<td>Lehmann -05</td>
<td>Lumiracoxib</td>
<td>1160</td>
<td>4</td>
<td>64.3</td>
<td>6.4 (4.2 to 8.6)</td>
<td>2, 4, 8, 13</td>
</tr>
<tr>
<td>Lund -98</td>
<td>Meloxicam</td>
<td>134</td>
<td>3</td>
<td>48.2</td>
<td>6.6 (1.4 to 11.8)</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>McKenna -01a</td>
<td>Celecoxib-diclofenac</td>
<td>400</td>
<td>3</td>
<td>69.1</td>
<td>8.8 (5.2 to 12.3)</td>
<td>2, 6</td>
</tr>
<tr>
<td>McKenna -01b</td>
<td>Celecoxib-etoaca</td>
<td>122</td>
<td>3</td>
<td>73.3</td>
<td>14.5 (2.7 to 26.3)</td>
<td>3, 6</td>
</tr>
<tr>
<td>Schnitzer -95</td>
<td>Nabumetone-etoaca</td>
<td>180</td>
<td>3</td>
<td>57.5</td>
<td>13.2 (5.4 to 21)</td>
<td>2, 4</td>
</tr>
<tr>
<td>Scott -00</td>
<td>Tiaprofenic acid</td>
<td>307</td>
<td>4</td>
<td>55.1</td>
<td>4.1 (4.0 to 4.2)</td>
<td>4</td>
</tr>
<tr>
<td>Sheldon -05</td>
<td>Lumiracoxib-celecoxib</td>
<td>1260</td>
<td>4</td>
<td>66.1</td>
<td>6.3 (2.9 to 8.7)</td>
<td>2, 4, 8, 13</td>
</tr>
<tr>
<td>Simon -98</td>
<td>Celecoxib</td>
<td>222</td>
<td>4</td>
<td>67.8</td>
<td>6.0 (−1.1 to 12.1)</td>
<td>1, 2</td>
</tr>
<tr>
<td>Tannenbaum -04</td>
<td>Lumiracoxib-celecoxib</td>
<td>1459</td>
<td>4</td>
<td>65.2</td>
<td>9.9 (4.6 to 15.2)</td>
<td>2, 4, 8, 13</td>
</tr>
<tr>
<td>Uzel -01</td>
<td>Flurbiprofen-tiaprofenic acid</td>
<td>26</td>
<td>3</td>
<td>61</td>
<td>17.0 (5.9 to 28.7)</td>
<td>3</td>
</tr>
<tr>
<td>Weaver -95</td>
<td>Nabumetone-oxaprozin</td>
<td>219</td>
<td>3</td>
<td>NA</td>
<td>12.5 (6.4 to 18.6)</td>
<td>1, 2, 4, 6</td>
</tr>
<tr>
<td>Williams -01</td>
<td>Celecoxib</td>
<td>472</td>
<td>4</td>
<td>66.4</td>
<td>7.5 (2.9 to 12.1)</td>
<td>2, 6</td>
</tr>
<tr>
<td>Williams -89</td>
<td>Etodolac</td>
<td>50</td>
<td>3</td>
<td>76</td>
<td>7.3 (6.0 to 14.6)</td>
<td>2, 4</td>
</tr>
<tr>
<td>Zhuo -99</td>
<td>Celecoxib</td>
<td>597</td>
<td>5</td>
<td>53.9</td>
<td>7.5 (4.8 to 10.2)</td>
<td>2, 12</td>
</tr>
</tbody>
</table>

Overall | 9964 | 3.8a | 64.3b | 10.2 (6.8 to 11.6) | 2.3a |

NA = not available.

a Mean.
b Weighted mean.
Oral NSAIDs in knee OA

Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials
Jan Magnus Bjordal, Anne Elisabeth Ljunggren, Atle Kløvning, Lars Slørdal

Withdrawal Symptoms

Patients, Doctors Explore Alternatives to Vioxx For Arthritis Relief -- Very Carefully
By January W. Payne
Washington Post Staff Writer
Tuesday, November 23, 2004; Page HE01

A new meta-analysis in the British Medical Journal (BMJ) recommends "only limited use" of NSAIDs for long-term treatment of knee osteoarthritis, citing questions about their effectiveness and safety. Of the 23 trials analyzed, all but one was short-term, evaluating the drugs' effects after two to 13 weeks. (The only longer-term study involved a drug not available in the United States.) A meeting of the Food and Drug Administration (FDA) drug safety advisory committee is planned for February to discuss the safety of the two other COX-2 drugs remaining on the U.S. market -- Bextra and Celebrex.
NSAID side effects
Implications of the relative degrees of Cox selectivity

Industry-funded NSAID-trials

Patient selection bias

1. Only patients who tolerate NSAID
2. Non-responders are tested and excluded
3. Effect size is inflated

Gottesdiener et al.
Rheumatology 2002
Paracetamol for low back pain and OA

Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials

Gustavo C Machado,¹ Chris G Maher,¹ Paulo H Ferreira,² Marina B Pinheiro,²

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical guidelines recommend paracetamol as first line analgesic drug for both spinal pain (neck and low back pain) and osteoarthritis of the hip and knee
The evidence base supporting these recommendations has recently been called into question

WHAT THIS STUDY ADDS

High quality evidence suggests that paracetamol is ineffective in reducing pain and disability or improving quality of life in patients with low back pain
There is high quality evidence that paracetamol offers a small but not clinically important benefit for pain and disability reduction in patients with hip or knee osteoarthritis
Though high quality evidence shows that patients taking paracetamol are nearly four times more likely to have abnormal results on liver function tests compared with those taking oral placebo, the clinical relevance of this is unclear
Pharmacological interventions for knee osteoarthritis

Effect over placebo for pharmacological interventions
(Maximum effect within 1 - 4 weeks)

Mean threshold "important improvement"

Mean threshold "slight improvement"

Mean threshold "minimal perceptible improvement"

Pain difference in mm on VAS over placebo

Oral NSAIDs including coxibs
Topical NSAIDs
Intra-articular steroid injection
Opioids
Paracetamol
Glucosamine sulphate
Chondroitin sulphate

Bjordal et al. (2)2007 Eur J Pain
[E-pub ahead of print May 6th]
The scientific evidence behind electrophysical agents is mounting.

The Pedro-database contains more than 2300 RCTs with EPAs and half of them have a method score of 6/10 or higher.

<table>
<thead>
<tr>
<th>Title</th>
<th>Method</th>
<th>Score</th>
<th>Select</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser therapy in the treatment of achilles tendinopathy: a pilot study</td>
<td>clinical trial</td>
<td>1/10</td>
<td>Select</td>
</tr>
<tr>
<td>The effect of 300 mW, 830 nm laser on chronic neck pain: a double-blind, randomized, placebo-controlled study</td>
<td>clinical trial</td>
<td>1/10</td>
<td>Select</td>
</tr>
<tr>
<td>Laser acupuncture for mild to moderate depression in a primary care setting -- a randomized controlled trial (with consumer summary)</td>
<td>clinical trial</td>
<td>1/10</td>
<td>Select</td>
</tr>
<tr>
<td>Low-level laser therapy for treatment of temporomandibular joint pain: a double-blind and placebo-controlled trial</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>Laser acupuncture in children with headache: a double-blind, randomized, bicenter, placebo-controlled trial</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>Double-blind randomized controlled trial of low-level laser therapy in carpal tunnel syndrome</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>A pilot study of laser-pointer laser therapy in the management of chronic neck pain</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>Treatment of postmastectomy lymphedema with low-level laser therapy: a double blind, placebo-controlled trial</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>Manipulations/behind of episodic tension-type headache; A randomized, controlled clinical trial (Unpubl.)</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>Low-level laser therapy in ankle sprains: a randomized clinical trial</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>The efficacy of low-level laser therapy in supraspinatus tendinitis</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
<tr>
<td>Low energy laser therapy in rheumatoid arthritis</td>
<td>clinical trial</td>
<td>9/10</td>
<td>Select</td>
</tr>
</tbody>
</table>

Numbers of Low-level laser therapy publications in Pubmed by year:

- 2000: 5
- 2001: 10
- 2002: 20
- 2003: 30
- 2004: 40
- 2005: 50
- 2006: 60
- 2007: 70
- 2008: 80
- 2009: 90
- 2010: 100
The scientific evidence behind electrophysical agents is mounting.

Improved EPA trial design quality opens for new and more robust conclusions.
Inflammation reduced after LLLT

A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E₂ concentrations

J M Bjordal, R A B Lopes-Martins, V V Iversen

TENS in acute low back pain

Method score PEDro: 8/10

**Table 3. Outcome Data after Transport**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 30)</th>
<th>Group 2 (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate—mean ± SD</td>
<td>67 ± 10 beats/min</td>
<td>99 ± 7 beats/min*</td>
</tr>
<tr>
<td>Systolic blood pressure—mean ± SD</td>
<td>136 ± 23 mm Hg</td>
<td>144 ± 21 mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure—mean ± SD</td>
<td>83 ± 14 mm Hg</td>
<td>87 ± 8 mm Hg</td>
</tr>
<tr>
<td>Pain score on VAS†—mean ± SD (95% CI)</td>
<td>49 ± 6 mm (43, 54)</td>
<td>77 ± 11 mm (73, 81)*</td>
</tr>
<tr>
<td>Anxiety score on VAS—mean ± SD (95% CI)</td>
<td>69 ± 12 mm (62, 75)</td>
<td>84 ± 9 mm (79, 81)*</td>
</tr>
</tbody>
</table>
Dose-response patterns have been identified and therapeutic windows determined.
EPAs & Osteoarthritis
OA: Characteristics & Progression

Prof G David Baxter TD DPhil MBA
Healthcare: Challenges

- Ageing Population
- Burden of Chronic Disease
- ICT - new forms of healthcare
- Patient-centred Care
- ‘Technology push’ of new services
- Training, regulation, accreditation etc

New Zealand Population

1980 versus 2030
Ageing Well & Longevity Dividend

Science for:
- Brain maintenance
- Reducing frailty
- Enabling environments
- Enhancing social support

Realising the Longevity Dividend
Osteoarthritis: Challenges

• Most prevalent form of arthritis globally
• Cardinal issue: cartilage loss
• Joints: hands, knees, hips and spine
• Deterioration over time: no ‘cure’
• ‘staying active, maintaining a healthy weight... may slow progression of the disease and help improve pain and joint function’

Mayo Clinic 2015
Cardinal Signs & Symptoms

- Pain (associated with movement)
- Joint Tenderness
- Stiffness (morning and inactivity)
- ‘Grating’
- Boney spurs
Patient Characteristics That Predict Progression of Knee Osteoarthritis: A Systematic Review of Prognostic Studies

CATHY M. CHAPPLE, HELEN NICHOLSON, G. DAVID BAXTER, AND J. HAXBY ABBOTT

**Objective.** To identify, by systematic review, patient characteristics that can be used by health care practitioners to predict the likelihood of knee osteoarthritis (OA) progression.

**Methods.** A search was conducted of the electronic databases Medline, EMBase, CINAHL, AMED, and Web of Science in November 2010. Two reviewers screened articles using inclusion/exclusion criteria. Study participants were adults with established knee OA. Outcome measures for disease progression were change in pain or function or deterioration in radiographic features. Included studies identified clinically relevant prognostic factors at baseline and reported a statistical association with outcome. Minimum followup was 1 year. Articles were assessed for bias, and strength of evidence was summarized for potential predictors of progression.

**Results.** Thirty studies were included, of which 26 were of high quality. Age, varus knee alignment, presence of OA in
OA Progression: Factors

Age
Varus Knee Alignment
Multiple Joint Involvement
BMI – long term progression >3 years
NB: Exercise not a predictor of progression

‘Few predictive variable have strong supporting evidence… variables with strong evidence easily evaluated and utilized in clinical practice’
Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness

J.H. Abbott †*, M.C. Robertson †, C. Chapple †, D. Pinto §, A.A. Wright ‖, S. Leon de la Barra ¶, G.D. Baxter #, J.-C. Theis †, A.J. Campbell †, On behalf of the MOA Trial team

† Centre for Musculoskeletal Outcomes Research, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
‡ Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
§ Physical Therapy and Human Movement Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
‖ Department of Physical Therapy, High Point University, High Point, NC, USA
¶ Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
# Centre for Physiotherapy Research, School of Physiotherapy, University of Otago, Dunedin, New Zealand
Treatment Success: Factors

- Posterior knee pain
- Disturbed sleep
- Absence of knee injury
- Instability
- Symptom duration (> 5 years)
- Female sex
PHYSIOTHERAPY IS ABOUT LIFE
Effect of low-level laser therapy on the expression of inflammatory mediators and on neutrophils and macrophages in acute joint inflammation

Ernesto Cesar Pinto Leal-Junior, Prof. PhD., PT.
Prof. Ernesto Cesar Pinto Leal Junior receives research support from Multi Radiance Medical™ (Solon, OH - USA), a laser therapy device manufacturer.
Background

Osteoarthritis is the most common adult joint disease and it has increasing in frequency and severity.

Estimated prevalence in USA - more than 25 million adults affected.

Disease progression is associated with cartilage degradation, joint space narrowing (JSN), and bony changes including osteophytes, subchondral sclerosis, and bone marrow lesion.¹

Background

In past, OA has traditionally been classified as a “non-inflammatory” arthritis.

However, currently it has been demonstrated that pro-inflammatory cytokines (acute phase) play an important role since they will have influence in MMPs.

MMPs play an important role in cartilage degeneration (chronic phase).²

Objective

Evaluate the effect of low-level laser therapy (LLLT) operating at 50 mW and 100 mW on joint inflammation induced by papain in rats.

- Histopathological analysis;
- Differential counts of inflammatory cells (macrophages and neutrophils);
- Gene expression of interleukin 1-beta and 6 (IL-1β and IL-6);
- Protein expression of Tumor Necrosis Factor alpha.
Methods

Sixty animals were randomly distributed into four groups of 15 animals each.

(control) did not receive any kind of intervention;

(injury), received induction but did not receive any treatment;

(LLLT 50 mW) was treated with LLLT - 50 mW;

(LLLT 100 mW) were treated with LLLT - 100 mW.

Evaluations/analyses - 24 hours after injury.
Papain-induced inflammation

The induction of OA was then performed following previously published methods.\textsuperscript{7,8}

20 μl injections were administered in the right knee of the hind leg of each animal

4% papain solution dissolved in 10 μl saline solution + 10 μl cysteine solution (0.03 M)


Low-level laser therapy (immediately after injection)

<table>
<thead>
<tr>
<th>Group</th>
<th>Wavelength (nm)</th>
<th>Type of diode laser</th>
<th>Mean Power Output (mW)</th>
<th>Spot Size (cm(^2))</th>
<th>Power Density (W/cm(^2))</th>
<th>Energy (J)</th>
<th>Energy Density (J/cm(^2))</th>
<th>Irradiation Time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mW</td>
<td>808</td>
<td>AsGaAl</td>
<td>50</td>
<td>0.028</td>
<td>1.78</td>
<td>4</td>
<td>142.4</td>
<td>80</td>
</tr>
<tr>
<td>100 mW</td>
<td>808</td>
<td>AsGaAl</td>
<td>100</td>
<td>0.028</td>
<td>3.56</td>
<td>4</td>
<td>142.4</td>
<td>40</td>
</tr>
</tbody>
</table>

GaAlAs - arsenide and aluminum gallium; LLLT - low-level laser therapy.
Sample collections

24 hours after induction

- Total and differentiated cell counts (neutrophils and macrophages);
- Histological procedures and histopathological analysis (HE);
- Evaluation of gene expression of inflammatory mediators (IL-1β and IL-6 mRNA) expression in articular synovial lavage;
- Evaluation of protein expression of TNF-α in articular synovial lavage.
Results

Total and differentiated cell counts (neutrophils and macrophages)

A and B (Control group);

C and D (Injury group): inflammatory infiltrate in articular space, and neutrophils;

E and F (50 mW): few inflammatory cells, and integrity of cartilage and meniscus;

G and H (100 mW): increased inflammation, and signs of degeneration;
Results

Evaluation of inflammatory mediators (IL-1β mRNA and IL-6 mRNA) expression in articular synovial lavage;

Evaluation of protein expression of TNF-α in articular synovial lavage
Conclusion

showed positive results, LLLT with 50 mW was more efficient in modulating inflammatory mediators (IL-1β, IL-6) and inflammatory cells (macrophages and neutrophils), and led to histological findings that indicate an attenuated inflammatory process.

These findings indicate that treatment with LLLT in early stages of OA (acute inflammatory phase) has the potential to decrease cartilage erosion in late
Effect of low-level laser therapy on the expression of inflammatory mediators and on neutrophils and macrophages in acute joint inflammation

Ana Carolina Araruna Alves, Rodolfo de Paula Vieira, Ernesto Cesar Pinto Leal-Junior, Solange Almeida dos Santos, Ana Paula Ligeiro, Regiane Albertini, Jose Antonio Silva Junior and Paulo de Tarso Camillo de Carvalho.
Effect of low-level laser therapy on metalloproteinase MMP-2 and MMP-9 production and percentage of collagen types I and III in a papain cartilage injury model

Ana Carolina Araruna Alves · Regiane Albertini · Solange Almeida dos Santos · Ernesto Cesar Pinto Leal-Junior · Eduardo Santana · Andrey Jorge Serra · José Antonio Silva Jr · Paulo de Tarso Camillo de Carvalho

Table 1 Low level laser therapy parameters

<table>
<thead>
<tr>
<th>Laser</th>
<th>AsGaAI</th>
<th>AsGaAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>DMC® - Photon Laser III</td>
<td>DMC® - Photon Laser III</td>
</tr>
<tr>
<td>Frequency</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
<tr>
<td>Power (mW)</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Power density (W/cm²)</td>
<td>3.5</td>
<td>1.78</td>
</tr>
<tr>
<td>Spot size (cm²)</td>
<td>0.028</td>
<td>0.028</td>
</tr>
<tr>
<td>Energy density (J/cm²)</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>Energy (J)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Time per point (s)</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Number of points</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Method</td>
<td>Transcutaneous</td>
<td>Transcutaneous</td>
</tr>
<tr>
<td>Place</td>
<td>Knee medial and lateral compartments</td>
<td>Knee medial and lateral compartments</td>
</tr>
<tr>
<td>Total energy (J)</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
Efficacy of low level laser therapy associated with exercises in knee osteoarthritis: a randomized double-blind study

Patricia Pereira Alfredo, Jan Magnus Bjordal, Silvia Helena Dreyer, Sarah Rúbia Ferreira Meneses, Giovana Zaguetti, Vanessa Ovanessian, Thiago Yukio Fukuda, Washington Steagall Junior, Rodrigo Álvaro Brandão Lopes Martins, Raquel Aparecida Casarotto and Amélia Pasqual Marques

Table 5. Within-group difference in change score (T1, T2 and T3) for laser and placebo groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups (n = 20/group)</th>
<th>T1 Mean (SD)</th>
<th>T2 Mean (SD)</th>
<th>T3 Mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Laser</td>
<td>5.32 (3.55)²</td>
<td>3.36 (3.47)³</td>
<td>2.58 (3.27)³</td>
<td>0.001²</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3.54 (3.06)</td>
<td>3.15 (2.94)</td>
<td>2.30 (2.25)</td>
<td>0.230</td>
</tr>
<tr>
<td></td>
<td><strong>Functionality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>11.88 (3.98)³</td>
<td>10.78 (4.62)³</td>
<td>8.37 (4.27)³</td>
<td>0.001³</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>11.55 (3.18)</td>
<td>10.68 (3.08)</td>
<td>10.40 (3.91)</td>
<td>0.400</td>
</tr>
<tr>
<td></td>
<td><strong>Range of motion (degree)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>91.50 (13.79)³</td>
<td>91.40 (12.11)³</td>
<td>99.45 (12.89)³</td>
<td>0.010³</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>91.80 (20.42)</td>
<td>95.65 (17.25)</td>
<td>96.55 (15.28)</td>
<td>0.180</td>
</tr>
<tr>
<td></td>
<td><strong>Muscle strength (H/kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>11.63 (4.87)</td>
<td>11.8 (4.86)</td>
<td>12.52 (4.50)</td>
<td>0.700</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>9.96 (3.58)</td>
<td>11.51 (6.62)</td>
<td>9.68 (3.65)</td>
<td>0.230</td>
</tr>
<tr>
<td></td>
<td><strong>Activity – WOMAC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pain subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>9.10 (4.92)²</td>
<td>6.55 (3.32)²</td>
<td>4.80 (4.36)²</td>
<td>0.000²</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>7.30 (3.54)</td>
<td>6.55 (3.98)</td>
<td>6.35 (3.48)</td>
<td>0.370</td>
</tr>
<tr>
<td></td>
<td><strong>Stiffness subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>3.05 (1.96)</td>
<td>2.35 (2.30)</td>
<td>2.35 (2.21)</td>
<td>0.720</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2.95 (2.14)</td>
<td>2.65 (2.23)</td>
<td>2.6 (2.11)</td>
<td>0.200</td>
</tr>
<tr>
<td></td>
<td><strong>Function subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>33.85 (16.93)²</td>
<td>24.15 (13.54)²</td>
<td>19.50 (14.04)²</td>
<td>0.000²</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>27.15 (11.32)</td>
<td>27.40 (13.88)</td>
<td>23.35 (12.18)</td>
<td>0.190</td>
</tr>
<tr>
<td></td>
<td><strong>Total score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser</td>
<td>46.05 (22.99)²</td>
<td>33.05 (18.62)²</td>
<td>26.65 (20.17)²</td>
<td>0.000²</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>38.00 (14.91)</td>
<td>36.60 (18.34)</td>
<td>32.30 (16.82)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*P-value for ANOVA
**Identify which values are statistically different between after multiple comparison test.

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
Adjunctive use of combination of super-pulsed laser and light-emitting diodes phototherapy on nonspecific knee pain: double-blinded randomized placebo-controlled trial

Ernesto Cesar Pinto Leal-Junior • Douglas Scott Johnson • Anita Saltmarche • Timothy Demehak
Take home message

Phototherapy is able to modulate inflammatory process in OA.

Modulatory effects in inflammatory cytokines and MMPs.

It is a very good EPA to be used in combination with exercises and other techniques.
Acknowledgements
Thanks!

ernesto.leal.junior@gmail.com
ernesto.leal.junior@multiradiance.com
Optimal electrical stimulation (ES) parameters for OA knee

Gladys Cheing, PhD
Professor & Associate Head
Department of Rehabilitation Sciences
The Hong Kong Polytechnic University
Osteoarthritis (OA) of the knee

**Prevalence:**
- Global prevalence of radiographically confirmed symptomatic knee OA: 3.8% in general population (Cross et al. 2014)
- For people aged over 70: 40% (Dieppe & Lohmander 2005)

Schematic drawing of an osteoarthritic joint (Bijlsma et al. 2011)
Common clinical symptoms of OA knee

- Knee pain
- Crepitus on active joint motion
- Morning stiffness lasting for 30 minutes or less
- Reduced range of motion
- Muscle weakness
- Physical function
osteoarthritis
stimulation
knee
electrical
Pain
controlled

Double
Currents
Painful
spatially
outcomes
improving

Effectiveness
Pulsed
mobility

Physical
management

TENS
Electro
hot

Function
status

Outcome
Intervention

Cure
Placebo

Electrode

Durations
Clinical

Intervention

Clinical
Targeted

Interventions
Electrical Stimulation for OA Knee

- Transcutaneous Electrical Nerve Stimulation (TENS)
- Interferential therapy (IFT)
- Electroacupuncture
- Microcurrent or pulsed subsensory threshold electrical stimulation
- Neuromuscular electrical stimulation (NMES)
Primary outcome. Efficacy for each intervention measured at the end of treatment. Mean difference over placebo for pain measured on a 100 mm visual analogue scale (VAS) is shown as columns, and error bars indicate 95% confidence limits. The horizontal dotted lines indicate subjective thresholds for mean perceptible improvement (lowest), mean slight improvement (middle) and mean important improvement (top).

Which form of ES is better?

TENS vs IFT (IFC)
Mechanisms of ES induced Analgesia

Gate Control Theory

Involvement of endogenous opioid

- Enkephalins
- β-endorphins
- Dynorphin
- Endomorphine
Experimental Pain
Fig. 3. The thermal pain threshold increased gradually from the baseline value to 105.2% in the transcutaneous electrical nerve stimulation (TENS ♦) group \((p = 0.004)\) and 105.0% in the interferential therapy (IFT ■) group \((p = 0.020)\) at 30 minutes into the stimulation. In contrast, there was no significant change in the heat pain threshold for the control group (▲). The between-group difference reached significance at 30min \((p = 0.017)\).
Stimulation Parameters

- Stimulation frequency
- Pulse width
- Waveform
- Stimulation mode: pulsed, modulation, burst
- Intensity
- Placement of electrode
- Stimulation duration
<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>N</th>
<th>Parameters of intervention</th>
<th>Results</th>
<th>Time point of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer et al. (2014)</td>
<td>G1:TENS + exercise &amp; education</td>
<td>G1:73</td>
<td>Intensity=&quot;strong but comfortable&quot; treatment time=&quot;as much as needed&quot; other parameters used depend on patients' preferences, modes for choices includes: -110Hz, 50μs -4Hz, 200μs -10Hz, 200μs -110Hz, 200μs -110Hz, 200μs, intensity modulated -frequency modulated, 200μs -burst mode with pulse frequency 100Hz, 200μs and burst frequency 2Hz Treatment period lasted for 6 weeks</td>
<td>No statistically significant differences between groups in WOMAC pain, stiffness, function and total scores, extensor muscle torque, global assessment of change, exercise adherence and exercise efficiency. Significant improvement over time is shown in all outcomes and improvement is maintained at 24-week follow up</td>
<td>Baseline 3 weeks 6 weeks 12 weeks 24 weeks</td>
</tr>
<tr>
<td>Atamaz et al. (2012)</td>
<td>G1:TENS sham</td>
<td>G1:37</td>
<td>Mode, waveform and pulse duration not reported, frequency=80Hz, intensity=10-30mA, 20 minutes on painful area, 15 treatment sessions over 3 weeks</td>
<td>Significant decrease in all assessment parameters over time No significant difference among the groups except WOMAC stiffness score and ROM. Intake of paracetamol was significantly lower in each treatment group when compared with the sham groups at 3 months. Subjects in IFC group used a lower amount of paracetamol at 6 months in comparison with the IFCs sham group.</td>
<td>Baseline 1 months 3 months 6 months</td>
</tr>
<tr>
<td>Vance et al. (2012)</td>
<td>G1:HF-TENS</td>
<td>G1:25</td>
<td>Mode not reported, asymmetrical biphasic pulses, frequency:G1:100Hz; G2:4Hz, pulse duration=100ms, 80 minutes on painful area, 1 Treatment session</td>
<td>Both HF-TENS and LF-TENS significantly increased Pressure Pain Threshold Placebo TENS had no significant effect on PPT Cutaneous pain measures were unaffected by TENS Subjective pain ratings at rest and during movement were similarly reduced by active TENS and placebo TENS</td>
<td>Baseline immediately after treatment</td>
</tr>
<tr>
<td>Study</td>
<td>Groups</td>
<td>N</td>
<td>Parameters of intervention</td>
<td>Results</td>
<td>Time point of measurement</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------------------</td>
<td>---------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Pietrosimone (2011)</td>
<td>G1:h-TENS + ex</td>
<td>G1:10</td>
<td>Continuous mode, biphasic pulses, frequency=150Hz, pulse duration=150ms, 8 hours on medial and lateral superior and medial and lateral inferior borders of patella, 12 treatment sessions over 4 weeks</td>
<td>- Quadriceps activation was significantly higher in the TENS with exercise group compared to the exercise only group at 2 weeks.</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>G2:placebo + ex</td>
<td>G2:10</td>
<td></td>
<td>- Quadriceps activation was significantly higher in the TENS with exercise group compared to the placebo group and exercise only group at 4 weeks.</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>G3:ex only</td>
<td>G3:11</td>
<td></td>
<td>- WOMAC scores improved in all 3 groups over time, with no significant differences among groups.</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Cheing &amp; Hui-Chan (2004)</td>
<td>G1:TENS</td>
<td>G1:16</td>
<td>Continuous mode, asymmetrical rectangular biphasic pulses, frequency=80 Hz, Pulse duration=140ms, 60 minutes on acupuncture points, 20 Treatment sessions over 4 weeks</td>
<td>- No significant difference between groups</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>G2:placebo stimulation</td>
<td>G2:16</td>
<td></td>
<td>- TENS + exercise group tended to produce greater cumulative increase in stride length, cadence and gait velocity</td>
<td>Session 10</td>
</tr>
<tr>
<td></td>
<td>G3:exercise</td>
<td>G3:15</td>
<td></td>
<td></td>
<td>Session 20</td>
</tr>
<tr>
<td></td>
<td>G4:TENS+ exercise</td>
<td>G4:15</td>
<td></td>
<td></td>
<td>4-week follow-up</td>
</tr>
<tr>
<td>Law &amp; Cheing (2004)</td>
<td>G1:TENS 2</td>
<td>G1:13</td>
<td>Mode and waveform not reported, G1:frequency=2Hz, pulse duration=576μs; G2:frequency=100Hz, pulse duration=200μs; G3:frequency alternates between 2 and 100 Hz, pulse duration alternate between 576 and 200 μs, all groups treated for 40 minutes on acupuncture points, 10 Treatment sessions over 2 weeks</td>
<td>- No significant between group differences</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>G2:TENS 100</td>
<td>G2:12</td>
<td></td>
<td>- Significant reduction in pain, time to complete TUG test and significant increase in knee PROM reported in active treatment groups</td>
<td>Day 5</td>
</tr>
<tr>
<td></td>
<td>G3:TENS 2/100</td>
<td>G3:13</td>
<td></td>
<td></td>
<td>Day 10</td>
</tr>
<tr>
<td></td>
<td>G4:Sham TENS</td>
<td>G4:10</td>
<td></td>
<td></td>
<td>2-week follow-up</td>
</tr>
<tr>
<td>Cheing et al. (2003)</td>
<td>G1:TENS2</td>
<td>G1:10</td>
<td>waveform not reported, continuous mode, frequency=100Hz, pulse duration=200μs, treated over acupuncture points, 10 Treatment sessions over 2 weeks, Treatment durations:G1:20 minutes; G2:40 minutes; G3:60 minutes</td>
<td>- 40 min is the optimal treatment duration of TENS, in terms of both the magnitude (VAS scores) of pain reduction and duration of post-stimulation analgesics for OA knee</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>G2:TENS40</td>
<td>G2:10</td>
<td></td>
<td></td>
<td>Day 5</td>
</tr>
<tr>
<td></td>
<td>G3:TENS60</td>
<td>G3:10</td>
<td></td>
<td></td>
<td>Day 10</td>
</tr>
<tr>
<td></td>
<td>G4:Placebo TENS60</td>
<td>G4:8</td>
<td></td>
<td></td>
<td>2-week follow-up</td>
</tr>
<tr>
<td>Cheing et al. (2002)</td>
<td>G1:TENS</td>
<td>G1:16</td>
<td>Mode not reported, square pulses, frequency=80Hz, pulse duration=140μs, 60 minutes on acupuncture points, 10 Treatment sessions over 4 weeks</td>
<td>- Significant reduction in pain score (VAS) across treatment session recorded in TENS and placebo TENS group</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>G2:Sham TENS</td>
<td>G2:16</td>
<td></td>
<td>- Reduction in knee pain is maintained in TENS and TENS+ exercise groups only</td>
<td>Session 10</td>
</tr>
<tr>
<td></td>
<td>G3:Exercise</td>
<td>G3:15</td>
<td></td>
<td></td>
<td>Session 20</td>
</tr>
<tr>
<td></td>
<td>G4:TENS+ exercise</td>
<td>G4:15</td>
<td></td>
<td></td>
<td>4-week follow-up</td>
</tr>
<tr>
<td>Study</td>
<td>Groups</td>
<td>Parameters</td>
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<td>Time point of measurement</td>
<td></td>
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<td>-------</td>
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<td>---------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| Atamaz et al. (2012) | G1: TENS sham  
G2: TENS  
G3: IFT sham  
G4: IFT  
G5: SWD sham  
G6: SWD | Sinusoidal wave, beat frequency=100Hz, carrier frequency=4000Hz, amplitude-modulated, intensity= tactile sensation threshold, 20 minutes on knee region, 15 treatment sessions over 3 weeks | - Significant decrease in all assessment parameters over time  
- No significant difference among the groups except WOMAC stiffness score and ROM.  
- Intake of paracetamol was significantly lower in each treatment group when compared with the sham groups at 3 months.  
- Subjects in IFC group used a lower amount of paracetamol at 6 months in comparison with the IFCs sham group | Baseline  
1 month  
3 months  
6 months |
| Gundog et al. (2012) | G1: 40Hz IFT  
G2: 100Hz IFT  
G3: 180 Hz IFT  
G4: Sham IFT | Waveform not reported, beat frequency: G1: 40Hz; G2: 100Hz; G3: 180Hz, carrier frequency=4000Hz, amplitude-modulated, intensity= "strong but comfortable", 20 minutes on lateral aspect of patella, 15 treatment sessions over 3 weeks | - Significant improvements in all variables in all groups over time, except WOMAC stiffness and range of motion after treatment and during follow-up  
- Improvement was greater in active IFT groups than sham treatment  
- Improvement in WOMAC stiffness was observed only in active IFT groups  
- No significant difference is found between active IFT treatment groups | Baseline  
3 weeks  
1 month |
| Adedoyin et al. (2005) | G1: TENS+exercise  
G2: IFT+exercise  
G3: exercise only | Waveform and carrier frequency not reported, Beat frequency=80Hz, continuous, intensity= "strong but comfortable", 20 minutes over either side of affected knee (electrode aligned longitudinally), 8 treatment sessions over 4 weeks | - Pain assessment score shown statistically significant decrease over time in all groups  
- Statistically significant improvement is recorded in WOMAC score over time in all groups | Baseline  
1 weeks  
2 weeks  
3 weeks  
4 weeks |
| Defrin et al. (2005) | G1: noxious adjusted IFT  
G2: noxious unadjusted IFT  
G3: innocuous adjusted IFT  
G4: innocuous unadjusted IFT  
G5: sham IFT  
G6: control | Sinusoidal wave, beat frequency=30-60Hz, carrier frequency=4000Hz, intensity: 30% above pain threshold in noxious IFT, 30% below pain threshold in innocuous IFT, 20 minutes on knee region, 12 treatment sessions over 4 weeks | - Both noxious and innocuous stimulation significantly decreased chronic pain and morning stiffness and significantly increased pain threshold and ROM compared with the control groups  
- Noxious stimulation decreased pain intensity and increased pain threshold significantly more than innocuous stimulation  
- No differences in treatment outcomes were found between adjusted and unadjusted stimulation | Baseline  
Post-treatment |
| Adedoyin et al. (2002) | G1: IFT, dietary advice and exercise  
G2: Control | Waveform and carrier frequency not reported, beat frequency=100Hz for 15 minutes, 80Hz for last 5 minutes, intensity= "mild sensation", 20 minutes on knee region, 8 treatment sessions over 4 weeks | - Significant differences between initial and final pain values in IFT and control is found  
- The pain rating in IFT group was found to be significantly better than that for the control | Baseline  
0.5 weeks  
1 weeks  
1.5 weeks  
2 weeks  
2.5 weeks  
3 weeks  
3.5 weeks  
4 weeks |
Optimal stimulation frequency of ES?

Various frequencies of TENS enhance the release of different endogenous opioids:

2 Hz: predominately enkaphalin

100Hz: predominately dynorphin

by Prof Han Ji-Sheng, Peking University, China

Hypothetical interaction of opioids (enkephalin and dynorphin) in the spinal cord of the rat (Han et al 1998)
N=34, received TENS either at: (i) 2 Hz; (ii) 100 Hz; (iii) an alternating stimulation frequency of TENS: 2 Hz and 100 Hz (2/100 Hz); or (iv) a placebo, 5 days a week for 2 weeks

Outcome measures: (i) VAS (ii) a timed up-and-go test; and (iii) knee ROM

Results: the 3 active TENS groups (2 Hz, 100 Hz, 2/100 Hz), but not the placebo group, significantly reduced osteoarthritic knee pain across treatment sessions

However, no significant between-group difference was found between the active TENS group

Placebo group: no significant reductions in any of the outcome measures

(Law & Cheing, J Rehabil Med 2004; 36: 220-225)
Alternating Frequencies of Transcutaneous Electric Nerve Stimulation: Does it Produce Greater Analgesic Effects on Mechanical and Thermal Pain Thresholds?

K. C. Tong, MSc, Sing Kai Lo, PhD, Gladys L. Cheing, PhD

Arch Phys Med Rehabil 2007;88:1344-9
During and shortly after electric stimulation, HPT increased significantly in the alternating frequency stimulation group \((P = 0.024)\) (Tong, Lo, Cheing 2007).
Duration of Stimulation

- From 20 min to 20 hours a day
- Develop tolerance effect
- ? optimal duration of stimulation
Optimal Stimulation Duration of TENS in the Management of OA knee pain

(Cheing et al. 2003) J Rehabil Med :35:62-68
Table II. Time (minutes) to reach half-life of transcutaneous electrical nerve stimulation (TENS) analgesia over the 10 days of treatment (mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>TENS&lt;sub&gt;20&lt;/sub&gt; (n = 10)</th>
<th>TENS&lt;sub&gt;40&lt;/sub&gt; (n = 10)</th>
<th>TENS&lt;sub&gt;60&lt;/sub&gt; (n = 10)</th>
<th>TENS&lt;sub&gt;PL&lt;/sub&gt; (n = 8)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day&lt;sub&gt;1&lt;/sub&gt;</td>
<td>162 ± 62</td>
<td>380 ± 77</td>
<td>352 ± 62</td>
<td>163 ± 73</td>
<td>1</td>
</tr>
<tr>
<td>Day&lt;sub&gt;2&lt;/sub&gt;</td>
<td>182 ± 58</td>
<td>316 ± 72</td>
<td>372 ± 61</td>
<td>148 ± 49</td>
<td>0</td>
</tr>
<tr>
<td>Day&lt;sub&gt;3&lt;/sub&gt;</td>
<td>178 ± 37</td>
<td>346 ± 63</td>
<td>270 ± 47</td>
<td>160 ± 79</td>
<td>1</td>
</tr>
<tr>
<td>Day&lt;sub&gt;4&lt;/sub&gt;</td>
<td>270 ± 50</td>
<td>350 ± 63</td>
<td>376 ± 67</td>
<td>58 ± 19</td>
<td>0</td>
</tr>
<tr>
<td>Day&lt;sub&gt;5&lt;/sub&gt;</td>
<td>196 ± 55</td>
<td>152 ± 47</td>
<td>330 ± 62</td>
<td>188 ± 68</td>
<td>1</td>
</tr>
<tr>
<td>Day&lt;sub&gt;6&lt;/sub&gt;</td>
<td>204 ± 40</td>
<td>246 ± 69</td>
<td>420 ± 64</td>
<td>253 ± 95</td>
<td>0</td>
</tr>
<tr>
<td>Day&lt;sub&gt;7&lt;/sub&gt;</td>
<td>198 ± 28</td>
<td>384 ± 66</td>
<td>348 ± 52</td>
<td>85 ± 28</td>
<td>0</td>
</tr>
<tr>
<td>Day&lt;sub&gt;8&lt;/sub&gt;</td>
<td>174 ± 38</td>
<td>336 ± 67</td>
<td>338 ± 64</td>
<td>150 ± 68</td>
<td>1</td>
</tr>
<tr>
<td>Day&lt;sub&gt;9&lt;/sub&gt;</td>
<td>196 ± 50</td>
<td>244 ± 49</td>
<td>360 ± 65</td>
<td>148 ± 72</td>
<td>1</td>
</tr>
<tr>
<td>Day&lt;sub&gt;10&lt;/sub&gt;</td>
<td>168 ± 32</td>
<td>256 ± 35</td>
<td>258 ± 49</td>
<td>35 ± 7</td>
<td>0</td>
</tr>
</tbody>
</table>

N = number of observations showing half-life being longer than 10 hours after stimulation.

(Cheing et al. 2003) J Rehabil Med :35:62-68
Placement of Electrode

**Painful area**

**Trigger point:**
- Hyperirritable spot in skin, fascia, tendon etc
- Produce a characteristic pattern of usual pain/symptom

**Acupuncture point:**
- A tender site on the body surface used for Chinese acupuncture
- Low pain threshold along meridian
- Many located over superficial branches of peripheral nerves

**Motor point:**
- Where peripheral motor nerve enter the surface of the muscle, may become tender in the myotome

**Dermatome, peripheral nerve, nerve plexus**
Placement of Electrode

A lot of overlap of the trigger point, acupuncture point, motor point with painful area. Clinical commonalities of these points:

- Tender to palpate
- Decrease resistance to electricity
- Production of refer pain on palpation
- A high-density input to CNS.
- When stimulate a trigger point, a motor nerve or acupuncture point is also likely to be stimulated
N=45 healthy subjects randomly assigned to receive either:
  (i) TENS with electrode placement on acupuncture points
  (ii) TENS on non-acupuncture points along a peripheral nerve; or
  (iii) no stimulation (control)
TENS parameters: 4 Hz, pulse duration of 200 μs for 30 minutes
Outcome Measures:
  Negative peak latency (NPL) in the sensory nerve conduction study of the right superficial radial nerve (SRN)
  Mechanical pain threshold (MPT)
  Mechanical pain tolerance (MPTol)
Results:
  Significant increases of NPL and MPT over time (p=0.015, 0.002) in the TENS groups
  No significant difference between the 3 groups in all outcome measures at any of the measurement points (all p > 0.05)

(Chan & Cheing 2005)
Electrical Stimulation:

Sensory stimulation (e.g. TENS, IFC) vs

Motor stimulation (e.g. NMES)
Does pain modulation improve motor function?

4 weeks of TENS alone produced:

- An average of 12.5% gain in isometric peak torque of the quadriceps in various knee positions
- 11.6% gain in stride length ($p=0.002$)
- 9% gain in cadence ($p=0.004$)
- 19.7% gain in gait velocity ($p=0.020$)

NB. No significant result was found in the placebo group

(Cheing & Hui-Chan 2004)
<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>N</th>
<th>Parameters of intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Laufer et al. (2014)          | G1: NMES + exercise, G2: exercise | G1:25 | NMES stimulation parameters not reported, ten contractions of quadriceps delivered at each session at maximal tolerated intensity, 12 treatment sessions over 6 weeks | - Significantly greater reduction in knee pain observed immediately after treatment in G1, which was maintained 12 weeks post-intervention in both groups  
- Both groups demonstrated an immediate increase in muscle strength and in functional abilities, with no differences between groups  
- Improvements in gait velocity and in self-report functional ability were maintained at the follow-up session  
- Improvements in muscle strength, time to up and go, and stair negotiation were not maintained |
| Imoto et al. (2013)           | G1: NMES + exercise, G2: exercise | G1:50 | NMES: Asymmetrical biphasic pulsed rectangular current, frequency=50Hz, pulse duration=250 μs, contraction time 10 s, rest time 30 s every 20 minutes; current intensity was the maximum tolerated by each patient, 16 treatment sessions over 8 weeks | - Statistically significant improvement in both groups was observed in all outcomes assessed  
- No statistically significant difference was found between the NMES + Ex and the Ex groups in NRS, TUG test and aspects of WOMAC: pain, function, and stiffness |
| Gabyzon et al. (2012)         | G1: NMES + exercise, G2: exercise | G1:25 | biphasic waveform, frequency=75Hz, pulse duration=200 μs, 10s on, 50s off, 2s ramp-up, no ramp-down. Intensity=maximum tolerable level, 10 reps are done per session, 12 treatment sessions over 6 weeks | - Decrease of pain is noted in both groups while decrease in G1 is significantly greater  
- All physical ability parameters improved significantly following both treatments with no significant differences between groups and no interaction effects. |
| Palmieri-Smith et al. (2010)  | G1: NMES, G2: Control          | G1:16 | NMES 3/week for 4 weeks. Waveform not reported, frequency 50 Hz, pulse width not reported, duty cycle ramp up 2 s, 10 s on–50 s off, intensity adjusted to at least 35% of MVC. 10 QF contractions Control group: no treatment; standard of care | - No significant difference in quadriceps femoris strength or activation for intervention group versus the control group  
- No significant difference between groups in terms of WOMAC scores  
- No significant difference between groups for 40-foot walk |
| Burch et al. (2008)           | G1: IF + NMES, G2: TENS        | G1:54 | For both groups 35 min therapy was applied daily for 8 weeks. G1: 15 min of IF followed by 20 min of NMES. IF 5000 Hz and premodulated beat frequency sweeping between 1 and 150 Hz. NMES parameters: biphasic square wave, frequency 50 Hz, duty cycle ramp up 2 s, 10 s on–50 s off, intensity adjusted to at least 35% of MVC. 10 QF contractions Group 2: 35 min of TENS, biphasic square wave with a 0.2 Hz frequency, amplitude of 60 mA, pulse width adjusted to give peak output of 73 nC | - Significantly greater reductions in WOMAC pain, stiffness and function subscales in IF + NMES group  
- IF + NMES group had a greater, but non-significant decrease in overall pain  
- The mean change from baseline to follow-up in the quality of life VAS ratings were similar between the two groups |
<table>
<thead>
<tr>
<th>Study</th>
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<th>N</th>
<th>Parameters of intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kocaman et al. (2008)</td>
<td>G1:NMES, G2:exercise</td>
<td>G1:19</td>
<td>NMES: 23 min 5 times/week for 4 weeks. Stimulation parameters not reported</td>
<td>- Significant improvements in pain, thigh circumference, activity time, CSA of RF and Lequesne and WOMAC indices in both groups, no significant differences between the groups</td>
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<tr>
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<td>G2:19</td>
<td>Exercise: Maximal quadriceps contractions: 3 sets of 10 repetitions. 5 times/week for 4 weeks</td>
<td>- Significant improvement in active knee range of motion in both groups, the improvement in the exercise group was more prominent</td>
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<tr>
<td>Durmus et al. (2007)</td>
<td>G1:NMES, G2:isometric exercise</td>
<td>G1:25</td>
<td>For both groups 20 min therapy was applied 5 days/week for 4 weeks</td>
<td>- Both groups showed significant improvements in VAS and WOMAC pain, physical function and stiffness scores, 50 m walking time and 10 step stair climb, 1RM and 10RM</td>
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<tr>
<td></td>
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<td>G2:25</td>
<td>Group 1: Asymmetric biphasic wave, frequency 50 Hz, pulse width 200 µs, duty cycle 10 s on–10 s off, intensity 70–120 mA</td>
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<td>Group 2: Isometric contractions held for 10 s, 50 s relaxation. Patient asked to increase the visual and auditory signals that she perceived at every contraction</td>
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<td></td>
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<td>No significant difference between the groups in any measure after therapy</td>
</tr>
<tr>
<td>Gaines (2004)</td>
<td>G1:NMES, G2:education</td>
<td>G1:20</td>
<td>Group 1: Biphasic rectangular wave, frequency 50 Hz, pulse width not reported, ramp up 3 s 10 s on–50 s off, intensity for first 4 weeks at 10–20% MVC, weeks 5–8 20–30% MVC, weeks 9–1230–40% MVC. 15 min duration. Electrodes (4 in × 5 in) positioned over the vastus medialis oblique and proximal vastus lateralis</td>
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<td>G2:18</td>
<td>Group 2: Arthritis self-help course, 12 hours of community-based education</td>
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<td>- Significant decrease in knee pain after an NMES session</td>
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<td></td>
<td>- No significant difference between groups in pain on the PPI and the PRIT following the intervention</td>
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<td></td>
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<td></td>
<td>- Non-significant 7% increase in pain for the NMES group and a significant 66% increase in pain for the education-only group on the AIMS2</td>
</tr>
<tr>
<td>Rosemffet et al. (2004)</td>
<td>G1:NMES, G2:Exercise, G3:NMES +Exercise</td>
<td>G1:8</td>
<td>Group A: NMES, 3 times/week for 30 min monophasic wave, 0.2 mlsg</td>
<td>- VAS pain improved significantly in all 3 groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G2:10</td>
<td>Amplitude, frequency 25 Hz, pulse width not reported, duty cycle 5 s on–5 s off, voltage 60–80V</td>
<td>- WOMAC indices improved significantly in all 3 groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G3:8</td>
<td>Group B: exercise programme, 1 h15 min twice a week</td>
<td>- QF torque improved significantly in G2 and G3</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Group C: Combined NMES and exercise</td>
<td>- Walk test improved significantly in G2 only</td>
</tr>
</tbody>
</table>
Take Home Message

- Therapeutic “window” concept applies to almost all kinds of interventions (e.g. pharmacotherapies, exercise therapy or manual therapy)

- If the dosage (or parameter) is:
  - Too low → insufficient energy input to achieve an effect
  - Too high → excessive energy input, no positive response
  - Deviation outside the window → may lead to a zero effect, or even an adverse effect

- However, very few studies have evaluated the optimal parameters for electrophysical agents
Acknowledgements

Collaborators

- Prof Christina Hui-Chan
- Prof Ji-Sheng Han
- Prof Kai-Ming Chan
- Prof Sing-Kai Lo

Postgraduate students

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- Hassen Tong
Thank You !
References


References


